that are recognized but, instead, the hydrogen peroxide produced when urate is degraded by urate oxidase (uricase). Because mice express urate oxidase, hydrogen peroxide may be the murine "ultimate danger signal." However, some questions remain. Is the effect specific to hydrogen peroxide, or do other reactive oxygen species such as hydroxyl or superoxide suffice? Is there a role for catalase and glutathione peroxidase, which rapidly degrade hydrogen peroxide? Knockout mice lacking xanthine oxidase have been generated (but they are "runted" and die by six weeks of age)[2]; do they lack the ability to respond to danger signals? Can human cells respond to urate crystals? Can such cells respond to reactive oxygen species, or was this pathway sacrificed when xanthine oxidase expression was lost? All these questions can be approached experimentally. We look forward to the answers and suspect that further complexity awaits.

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## Autism and DPT Vaccination in the United Kingdom

**TO THE EDITOR:** On the basis of information recorded in the General Practice Research Database in the United Kingdom, we previously reported that the risk of receiving a diagnosis of autism between two and five years of age was four times as high among boys born in 1993 as among boys born in 1988.[1] We presented evidence that this increase had no relation to the use of mumps, measles, and rubella vaccine, a finding similar to that reported by Madsen et al. in the *Journal* in a study based on data from Denmark.[2] We recently reported on a study of 126 cases of autism in boys two to four years of age who were born between 1990 and 1998 and 624 controls (matched for age, sex, general practice, and the index date of the case), in which we found evidence that the increase in the incidence of autism in the United Kingdom was related to changes in diagnostic practices.[3]

Because it has been proposed that the development of autism may be associated with exposure to mercury in vaccines containing the preservative thimerosal, we further analyzed data from our recent case–control study to evaluate the effects of exposure to diphtheria, pertussis, and tetanus (DPT) vaccines, which are the only thimerosal-containing vaccines routinely used in the United Kingdom. Since 1990, it has been recommended that DPT vaccination be given at two, three, and four months of age in the United Kingdom.

For this analysis, we excluded 4 of 126 patients with autism (and their controls) and 17 additional controls for whom we could not ascertain the primary DPT vaccination schedule because the child's medical history was not recorded in the General Practice Research Database from the time of birth. Among the remaining 122 patients with autism and 587 controls, 117 patients (96 percent) and 561 controls (96 percent) had three primary DPT vaccinations. Three DPT vaccinations were recorded by six months of age in 112 of the patients (92 percent) and 518 of the controls (88 percent), which was not a significant difference (odds ratio, 1.6; 95 percent confidence interval, 0.7 to 3.3; P=0.23). The same proportion of patients (2 percent) as controls (2 percent) received separate component vaccines as their primary immunization (e.g., three diphtheria–tetanus vaccinations and three pertussis vaccinations).

Our results are in close agreement with a separately conducted cohort analysis of data from the General Practice Research Database, recently presented by Elizabeth Miller to the U.S. Institute of Medicine,[4] which showed no evidence of an increased risk of autism or other developmental problems related to exposure to thimerosal in vaccines

given to infants in the United Kingdom. Taken together, these findings provide further support for the view that exposure to mercury in vaccines is not the cause of the rising incidence of autism diagnosed in the United Kingdom during the past decade.

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*Editor's note:* The authors report serving as consultants to a law firm representing a vaccine manufacturer in litigation over alleged harm from exposure to vaccines.

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